REMARKS

I. Status of the Application

Claims 1, 2, 7-14 and 18-25 are pending in the application. New claim 37 has been added. Claims 1, 2, 7-14 and 18-25 remain rejected under 35 U.S.C. § 112, first paragraph. Claims 1 and 2 stand rejected under 35 U.S.C. § 112, second paragraph. Claims 1, 2, 7-9, 11-14 and 18-21 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Levine et al., U.S. Patent No. 6,171,798 in view of Chang et al. (1998) *Oncogene* 16:1921. Claim 10 remains rejected under 35 U.S.C. § 103(a) as unpatentable over Levine et al. in view of Chang et al. further in view of Ts'o et al., U.S. Patent No. 5,962,237. Applicants gratefully acknowledge that the rejection of claims 1 and 2 under § 102(b) has been withdrawn.

Applicants have amended the claims to more clearly define and distinctly characterize Applicants' novel invention. Support for the amendments can be found in the specification and the claims as originally filed. Specifically, support for the amendments to claims 1, 2, 7 and claim 22 to recite specific genes can be found in the specification at least at Figure 2A. Support for the amendments to these claims to recite a nucleic acid or marker that corresponds to a gene can be found in the specification at least at page 9, lines 18 and 26-27, where Applicants teach "suitable nucleic acid samples may contain transcripts of interest" and that "suitable samples include, but are not limited to, transcripts of the gene or genes," and at page 6, lines 16-17, where Applicants teach that markers "may include any nucleic acid sequence." Support for the amendments to claim 1 to recite a first gene and a second gene that are associated with oral cancer can be found in the specification at least at page 2, lines 12-15, where Applicants teach "expression levels of genes associated with a cell sample are identified and then analyzed and/or compared with known expression levels of genes for malignant and/or normal cells." Support

for new claim 37 can be found at least in claims 7 and 8 as originally filed. The claims were further amended to correct formal matters. The amendments presented herein add no new matter.

Applicants respectfully request entry and consideration of the foregoing amendments, which are intended to place the case in condition for allowance.

II. Formal Matters

At page 2, paragraph 3 of the instant Office Action, the Examiner has noted that Applicants' amendment filed February 23, 2004 contained a typographical error in the paragraph beginning on page 19, line 19. In response, Applicants respectfully submit that the specification has been amended to underline SUPERSCRIPT™, and to delete "Superscript".

III. Claims 1, 2, 7-14 and 18-25 Are Enabled

At page 2, paragraph 4 of the instant Office Action, claims 1, 2, 7-14 and 18-25 remain rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner states that while it is clear from the teachings of Applicants' specification that a ***particular subset*** of genes are in fact differentially expressed in oral cancer tissues as compared to normal oral tissue, the claims as written encompass the identification of virtually any gene as being associated with oral cancer and/or differentially expressed. The Examiner also states that with regard to claim 7 and claims dependent therefrom, while it is clear from the teachings of the specification that detection of expression levels of ***certain genes*** would aid in oral cancer diagnosis, this would not be the case for any gene associated with oral cancer. Applicants respectfully traverse these rejections in view of the amended claims now presented.

Without acquiescing to the Examiner's rejections, Applicants respectfully submit that the pending claims have been amended to recite individual genes that are differentially regulated in oral cancer. Specifically, claims 1, 2, 7 and 22 have been amended to recite ***thirteen particular genes*** which Applicants have discovered to be differentially regulated in oral tumor tissues. Applicants have provided a GenBank Accession Number which provides the mRNA sequence that corresponds to each of the claimed genes.

Applicants incorporate herein the arguments presented in the Amendment and Response filed February 23, 2004. Briefly, Applicants reiterate that the specification teaches how to prepare nucleic acid samples, how to analyze nucleic acid samples using microarrays, and how to analyze raw data obtained by microarray experimentation using software such as GENECHIP software, GeneCluster SOM and MATLAB™. Given the recitation of particular genes in view of the teachings of the specification, Applicants respectfully submit that one of skill in the art would be able to make and use the invention without undue experimentation.

Thus, the specification provides adequate written description under 35 USC § 112, first paragraph, for the claimed subject matter. Accordingly, Applicants respectfully request that the rejection of claims 1, 2, 7-14 and 18-25 under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

IV. Claims 1 and 2 Are Definite

At page 4, paragraph 5 of the instant Office Action, claims 1 and 2 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants' regard as the invention. Applicants respectfully traverse this rejection of the claims as amended herein.

The Examiner asserts that claim 1 is indefinite over the recitation of the phrase "wherein a gene that hybridizes differently is associated with oral cancer." The Examiner notes that the method steps of claim 1 refer to hybridization of probe arrays with populations of nucleic acids, but never mention or refer to hybridization of a gene or genes. The Examiner concludes that it is unclear as to how the practice of the recited method steps could or would result in identifying a "gene" that "hybridizes differently" and is associated with oral cancer, and requests clarification. In response, Applicants have amended claim 1 to clarify that the nucleic acid corresponds to a gene associated with oral cancer, thus obviating this rejection.

The Examiner asserts that claim 2 is indefinite over the recitation "the binding of the second array of probes" because there is insufficient antecedent basis for this limitation in the claim. In response, Applicants submit that claim 2 to remove "the" from the phrase "the binding of the second array of probes," thus obviating this rejection.

Accordingly, Applicants submit that the pending claims are definite. Therefore, Applicants respectfully request that the rejection of claims 1 and 2 under 35 U.S.C. § 112, second paragraph be reconsidered and withdrawn.

V. Claims 1, 2, 7-9, 11-14 and 18-21 Are Nonobvious Over Levine et al. in view of Chang et al.

At page 5, paragraph 10 of the instant Office Action, claims 1, 2, 7-9, 11-14 and 18-21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Levine et al., U.S. Patent No. 6,171,798, in view of Chang et al. (1998) *Oncogene* 16:1921. The Examiner is of the opinion that Levine et al. discloses methods of diagnosing cancer in a subject in which the level of expression of one or more cancer markers in a subject is compared to marker levels in a control, wherein a significant difference in levels is indicative of cancer. The Examiner acknowledges

that Levine et al. do not specifically teach detection of oral cancer, or teach the use in their method of cells obtained from oral tissue. The Examiner asserts that Chang et al. teaches a group of genes that are differentially expressed in oral cancer cells as compared to normal cells. The Examiner concludes that the combined references of Levine et al. and Chang et al. suggest all the limitations of the instant claims, and therefore maintains the rejection. Applicants respectfully traverse these rejections in view of the amended claims now presented.

Applicants' claims are directed to a method of identifying genes associated with oral cancer, a method of monitoring gene expression, a method of diagnosing a human subject with oral cancer, and a method of monitoring the progression of oral cancer, wherein a nucleic acid or marker that corresponds to a gene is detected, and wherein the gene is p-53 responsive gene 2 (GenBank Accession Number D86983), matrix metalloproteinase 1 (GenBank Accession Number X54925), beta A inhibin (GenBank Accession Number X57579), human alpha-1 collagen type I gene (GenBank Accession Number M55998), GRO1 oncogene (GenBank Accession Number X54489), mitochondrial 1 creatine kinase (GenBank Accession Number J04469), placental protein 11 (GenBank Accession Number M32402), BENE protein (GenBank Accession Number U17077), keratin 4 (GenBank Accession Number X07695), keratin 15 (GenBank Accession Number X07696), neuromedin U (GenBank Accession Number X76029), flavin containing monooxygenase 2 (GenBank Accession Number Y09267) or interleukin 1 receptor antagonist (GenBank Accession Number X53296). Thus, Applicants provide methods by which specific markers may be used to identify genes associated with oral cancer and to diagnose and monitor oral cancer.

The combination of references cited by the Examiner fails to teach or suggest each and every element of the claimed invention. Levine et al. fails to teach or suggest the claimed

invention. Levine et al. is directed to monitoring p53 related genes in a cell. The Examiner recognizes that that Levine et al. does not specifically teach detection of oral cancer and does not teach the use of their method in cells obtained from oral tissue.

The Examiner uses Chang et al. to cure the deficiencies of the primary reference. Although Chang et al. is directed to the characterization of transformation-related genes in oral cancer, this reference neither teaches nor suggests that any of the presently claimed genes are associated with oral cancer. Based on the teachings of these references, alone or in combination, one of skill in the art would not arrive at Applicants' claimed invention.

Thus, Levine et al. in view of Chang et al. fails to teach each and every element of the claimed invention and fails to render the claimed invention obvious. Accordingly, Applicants request that the rejection of claims 1, 2, 7-9, 11-14 and 18-21 under 35 U.S.C. § 103(a) over Levine et al. in view of Chang et al. be reconsidered and withdrawn.

VI. Claim 10 Is Nonobvious Over the Cited Art

At page 7, paragraph 8 of the instant Office Action, claim 10 remains rejected under 35 U.S.C. § 103(a) as being unpatentable over Levine et al. in view of Chang et al., further in view of Ts'o et al, U.S. Patent No. 5,962,237. The Examiner is of the opinion that the Ts'o et al. reference teaches that cancer cells present in the blood are indicative of cancer metastasis, and that the reference discloses methods for enriching such cells so as to facilitate detection of cancer metastasis. The Examiner concludes that the combined references of Levine et al., Chang et al. and Ts'o et al. suggest all the limitations of claim 10. Applicants respectfully traverse this rejection based on claim 10 as amended.

The combination of Levine et al. and Chang et al. fails to render the invention obvious for the reasons set forth above. Ts'o et al. fails to cure the deficiencies of the primary references. Ts'o et al. is directed to methods for enriching rare cells in a fluid. Ts'o et al. does not teach or suggest comparing expression of a marker in a test sample and a control sample from the same subject wherein the marker corresponds to any of the claimed genes. Accordingly, as none of the cited references teach Applicants' claimed invention, Applicants request that the rejection of claim 10 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

VII. Conclusion

Having addressed all outstanding issues, Applicants respectfully request reconsideration and allowance of the case. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is requested to telephone the undersigned at the number below.

Respectfully submitted,

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